# Exhibit A
# Amgen's Contested Issues of Fact

## III. CONTESTED ISSUES OF FACT

### A. Amgen's Contested Issues of Fact[1]

#### 1. Infringement[2]

1. Whether the preponderance of the evidence shows that Roche's importation of its peg-EPO product infringes, either literally or under the doctrine of equivalents, claims 1 and 2 of the Lin '868 patent.

2. Whether the preponderance of the evidence shows that Roche's importation of its peg-EPO product infringes, either literally or under the doctrine of equivalents, claims 7-9 of the Lin '698 patent.

3. Whether the preponderance of the evidence shows that Roche's importation of its peg-EPO product infringes, either literally or under the doctrine of equivalents, claim 7 of the Lin '349 patent.

4. Whether the preponderance of the evidence shows that Roche's peg-EPO product infringes, either literally or under the doctrine of equivalents, claims 7-9, 11, 12, and 14 of the Lin '933 patent.

#### 2. Invalidity

5. Whether Roche has presented clear and convincing evidence that shows that the following claims of the patents-in-suit are anticipated: (a) claims 1 and 2 of the Lin '868 patent, (b) claims 6-9 of the Lin '698 patent, (c) claim 7 of the Lin '349 patent, (d) claims 3, 7-9, 11, 12, and 14 of the Lin '933 patent, and (e) claim 1 of the Lin '422 patent.

6. Whether Roche has presented clear and convincing evidence that the following claims of the patents-in-suit are rendered obvious as of the date(s) they were invented by Dr. Lin: (a) claims 1 and 2 of the Lin '868 patent, (b) claims 6-9 of the Lin '698 patent, (c) claim 7 of the Lin '349 patent, (d) claims 3, 7-9, 11, 12, and 14 of the Lin '933 patent, and (e) claim 1 of the Lin '422 patent.

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[1] Based on the Court's claim construction, both parties' motions for summary adjudication, Roche's responses to Requests for Admission and Roche's Responses to Amgen's 56.1 Statements accompanying Amgen's Motions for Summary Judgment, Amgen believes that the facts listed below, with the exception of facts 1-11, are beyond genuine dispute or have been adjudicated by the Court. Amgen has listed facts 12 – 245 as "contested facts" because Roche does not agree these facts are undisputed or established and has refused to stipulate to them. This is not an exhaustive list of all of the factual issues Amgen intends to present at trial.

[2] Based on the Court's claim construction and Amgen's pending motions for summary judgment, Amgen believes there are no facts in dispute regarding infringement of '422 claim 1, '933 claim 3 and '698 claim 6, and that Amgen is entitled to summary judgment of infringement.

7. Whether Amgen has demonstrated the existence of objective indicia of non-obviousness, including for example whether any of the indicia listed below tends to show that the asserted claims are not obvious:

- Commercial success by way of adoption of and demand for EPOGEN®;
- A long felt, unmet need in the art that was satisfied by the claimed inventions;
- The failure of others to make the inventions;
- Copying of the claimed inventions by others in the field;
- Unexpected results achieved by the claimed inventions;
- Praise of the inventions by others in the field;
- The taking of licenses under the patents by others;
- Expressions of surprise by others in the field of the making of the inventions, or
- The patentee proceeding contrary to the accepted wisdom indicated by the prior art.

8. Whether Roche has presented clear and convincing evidence showing that as of the time of Dr. Lin's inventions, applying the teachings of Lin's specifications, one of ordinary skill in the art would not have been able to practice the following inventions without undue experimentation: (a) claims 1 and 2 of the Lin '868 patent, (b) claims 6-9 of the Lin '698 patent, (c) claim 7 of the Lin '349 patent, (d) claims 3, 7-9, 11, 12, and 14 of the Lin '933 patent, and (e) claim 1 of the Lin '422 patent.

9. Whether Roche has presented clear and convincing evidence showing that the specification of the patents-in-suit does not reasonably convey to those of ordinary skill in the art that the inventor had possession of the following inventions as of the date of his completed application for patent: (a) claims 1 and 2 of the Lin '868 patent, (b) claims 6-9 of the Lin '698 patent, (c) claim 7 of the Lin '349 patent, (d) claims 3, 7-9, 11, 12, and 14 of the Lin '933 patent, and (e) claim 1 of the Lin '422 patent.

### 3. Unenforceability[3]

10. Whether Roche has shown by clear and convincing evidence that individuals associated with the filing or prosecution of the patents-in-suit withheld or misrepresented information from the U.S. PTO that was material to the prosecution of the claimed inventions in each patent-in-suit.[4]

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[3] As noted in Section IX, Amgen believes that inequitable conduct issues should be tried to the Court.

[4] Roche's Statement of Contested Facts contains numerous facts relating to inequitable conduct that were not included in Roche's First Amended Answer. This Court has already rejected Roche's attempts to amend its pleadings. *See* June 7, 2007 Order Denying [445] Motion to Amend its Answer to Amplify Allegations of Amgen's Inequitable Conduct and to Define Relevant Markets for Purposes of Antitrust Counterclaims; *see also* July 18, 2007 Order Denying [631] Motion to Amend Pleadings to Conform to the Evidence. Amgen intends to file

11. Whether Roche has shown by clear and convincing evidence that the information withheld or misrepresented was withheld or misrepresented with the intent to deceive the PTO.

**4. Basic facts about the parties**

12. Amgen Inc. is a Delaware corporation with its principal place of business in Thousand Oaks, California.

13. F. Hoffmann-LaRoche Ltd. is a Swiss company with its principal place of business in Basel, Switzerland.

14. Roche Diagnostics GmbH is a German company with its principal places of business in Penzberg, Germany and Mannheim, Germany.

15. Hoffman LaRoche Inc. is a New Jersey Corporation with its principal place of business in Nutley, New Jersey.

16. This Court has jurisdiction over the claims asserted in Amgen's Amended Complaint pursuant to 28 U.S.C. §§ 1338(a) and 2201-02. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391 and 1400(b).

17. This action was commenced by Amgen on November 8, 2005.

18. Amgen manufactures and sells a recombinant human erythropoietin product, epoetin alfa, under the tradename Epogen®.

**5. Long-felt, unmet need**

19. Since the 1950s, researchers sought to conduct experiments with preparations containing naturally occurring EPO to determine if it had any therapeutic effectiveness, but such experiments were hampered by a lack of supply of EPO from natural sources.

20. "[I]n light of the complications associated with the then existing forms of treatment for the anemia of chronic renal failure, there was a need for an alternative therapy." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 126-27 (D. Mass. 2001).

21. "[P]rior to Amgen's path breaking invention, there was a long-felt need for a human EPO preparation that was therapeutically effective in treating the anemia of chronic renal failure." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d at 128.

22. Prior to Lin's invention, researchers around the world repeatedly attempted and failed to isolate or make an EPO product effective in treating patients with anemia.

23. Roche is aware of no anemic patient whose anemia was corrected by the administration of urinary erythropoietin.

24. Roche is aware of no anemic patient whose anemia was corrected by the administration of EPO-containing plasma.

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a *motion in limine* requesting that this evidence be excluded.

25. "[T]he need for the mass production of EPO had existed for 'many, many years'" prior to Dr. Lin's inventions. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d at 126 (D. Mass. 2001).

26. "[U]ntil the advent of Amgen's recombinant EPO product, the anemia associated with chronic renal failure remained uncorrected." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d at 127.

27. Before the advent of Amgen's recombinant EPO product, whether EPO could actually produce a sustainable increase in a patient's hematocrit was not known.

**6. Failure of others**

28. Although researchers all across the globe sought to fulfill the long-felt need for a human EPO preparation that was therapeutically effective, Amgen was the first to succeed.

29. "Many skilled artisans tried unsuccessfully to achieve Dr. Lin's inventions." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202, 319 (D. Mass 2004).

30. Many parties were racing to clone the human EPO gene and express in vivo biologically active recombinant human erythropoietin, including Genetics Institute, Biogen, Genentech, and Dr. Stuart Orkin, and none of them accomplished any of these feats before Dr. Lin.

31. Genetics Institute scientists did not isolate a DNA encoding human EPO before May 30, 1984.

32. Genetics Institute scientists did not confirm that they had expressed *in vivo* biologically active EPO before September 1984.

33. NeoRecormon in human urine can be distinguished from endogenous EPO found in human urine.

34. EPOGEN in human urine can be distinguished from endogenous EPO found in human urine.

35. Cloned EPO DNA is necessary but not sufficient to produce an *in vivo* biologically active recombinant erythropoietin glycoprotein.

**7. Prior art facts**

36. The maximum reported specific activity of Dr. Goldwasser's purified urinary EPO is 70,400 U/mg.

37. The maximum reported specific activity of Roche's epoetin beta is in excess of 200,000 U/mg.

38. The maximum reported specific activity of Amgen's epoetin alfa is in excess of 174,000 U/mg.

39. The half-life of Dr. Goldwasser's urinary EPO in the human body is 0.11 to 0.472 hours.

40. No significant change in hematocrit was observed in any patient who was

administered Dr. Goldwasser's urinary EPO.

41. The distribution of erythropoietin glycoforms in human urine is different than the distribution of the glycoforms in either epoetin alfa or epoetin beta.

42. Before Dr. Lin's inventions, no one had successfully purified EPO from human plasma or serum.

43. Dr. Eschbach's administration of EPO-rich human plasma to a single patient occurred on Nov. 13, 1984.

**8. Lin's Inventions**

**a. Facts surrounding invention**

44. By October 1983, Amgen's Dr. Fu-Kuen Lin had cloned the EPO gene.

45. Dr. Eugene Goldwasser did not isolate or identify the gene encoding human erythropoietin.

46. Dr. Leroy Hood did not isolate or identify the gene encoding human erythropoietin.

47. Dr. Por Lai did not isolate or identify the gene encoding human erythropoietin.

48. "The successful cloning [by Dr. Lin] of the EPO gene took place in September or early October, 1983." *Amgen Inc. v. Chugai Pharm. Co.*, 1989 WL 169006 at *16 (D. Mass. Dec. 11, 1989).

49. "In late October, 1983, Dr. Lin cloned the monkey cDNA EPO sequence." *Amgen Inc. v. Chugai Pharm. Co.*, 1989 WL 169006 at *16 (D. Mass. Dec. 11, 1989).

50. "By January 10, 1984, Amgen had expressed human EPO in human embryonic kidney cells called "293" cells and in COS cells, which are monkey kidney cells." *Amgen Inc. v. Chugai Pharm. Co.*, 1989 WL 169006 at *16 (D. Mass. Dec. 11, 1989).

51. "On February 13 and 14, 1984, Amgen conducted experiments to show that the recombinant human EPO produced in the COS cell was biologically active." *Amgen Inc. v. Chugai Pharm. Co.*, 1989 WL 169006 at *16 (D. Mass. Dec. 11, 1989).

52. "From March 1-9, 1984, Amgen conducted an in vivo bioassay and determined that the recombinant EPO was biologically active." *Amgen Inc. v. Chugai Pharm. Co.*, 1989 WL 169006 at *16 (D. Mass. Dec. 11, 1989).

53. "On March 15, 1984, Lin obtained the human full length EPO cDNA gene." *Amgen Inc. v. Chugai Pharm. Co.*, 1989 WL 169006 at *16 (D. Mass. Dec. 11, 1989).

54. "By May 2, 1984, human rEPO had been expressed in CHO cells." *Amgen Inc. v. Chugai Pharm. Co.*, 1989 WL 169006 at *16 (D. Mass. Dec. 11, 1989).

**9. Immediate acceptance and recognition**

55. "The results of the first clinical trials with recombinant human EPO were dramatic beyond anyone's dreams." *Amgen Inc. v. Hoechst Marion Roussel*, 126 F. Supp. 2d 69, 116 (D. Mass. 2001).

56. "Amgen's invention opened the floodgates for EPO production and ultimately led to a therapeutically effective pharmaceutical composition containing human EPO." *Amgen Inc. v. Hoechst Marion Roussel*, 126 F. Supp. 2d 69, 116 (D. Mass. 2001).

57. "Amgen's EPO product, which was the first EPO-containing pharmaceutical composition to obtain FDA approval, has greatly improved the quality of life of chronic renal failure patients throughout the world." *Amgen Inc. v. Hoechst Marion Roussel*, 126 F. Supp. 2d 69, 116 (D. Mass. 2001).

58. Transfusion therapy for chronic renal patients, along with its various risks, became a thing of the past directly as a result of the safety and efficacy of recombinant human EPO.

59. Shortly following its introduction, recombinant human EPO therapy was widely accepted as the standard treatment for the anemia of chronic renal failure.

60. "Dr. Lin received widespread public acclaim for his work." *Amgen Inc. v. Hoechst Marion Roussel*, 126 F. Supp. 2d 69, 116 (D. Mass. 2001).

61. Others, including Ortho (part of Johnson & Johnson), acknowledged the validity of Dr. Lin's patents in suit and sought and received a license under them.

**10. J&J License**

62. On September 30, 1985, Amgen granted Ortho Pharmaceutical Corporation a license to commercialize recombinant human erythropoietin as a human therapeutic in the United States for all uses other than dialysis and diagnostics.

63. In the United States, all recombinant human erythropoietin sold by Ortho is manufactured by Amgen and sold by Ortho under the trademark PROCRIT® (Epoetin alfa).

64. PROCRIT® brand Epoetin alfa is identical to EPOGEN® brand Epoetin alfa, which is manufactured by Amgen.

65. Pursuant to the Product License Agreement with Ortho, Amgen earns a 10% royalty on sales of PROCRIT® by Ortho in the United States.

**11. The Lin Patents**

**a. Filings**

66. Dr. Fu-Kuen Lin is the inventor of the inventions claimed in the '868, '933, '698, '349 and '422 patents.

67. The '868, '933, '698, '349 and '422 patents share a common disclosure.

68. The '868, '933, '698, '349 and '422 patents each claim priority from the following common applications: U.S. Patent Application Serial No. 675,298 (November 30, 1984), which is a continuation-in-part of U.S. Patent Application Serial No. 655,841 (September 28, 1984), which is a continuation-in-part of U.S. Patent Application Serial No. 582,185 (February 21, 1984), which is a continuation-in-part of U.S. Patent Application Serial No. 561,024 (December 13, 1983).

69. U.S Patent Application No. 561,024 ("the '024 application") was filed on

December 13, 1983.

70. U.S. Patent Application No. 582,182 ("the '182 application") was filed on February 21, 1984 and is a continuation-in-part application of the '024 application.

71. U.S. Patent Application No. 655,841 ("the '841 application") was filed on September 28, 1984 and is a continuation-in-part application of the '182 application.

72. U.S. Patent Application No. 06/675,298 ("the '298 application") was filed on November 30, 1984 as a continuation-in-part of the '841 application and issued as U.S. Patent No. 4,703,008 on October 27, 1987.

73. The '868 patent issued from United States Patent Application No. 113,179 ("the '179 application"), filed October 23, 1987, which is a continuing application of United States Patent Application No. 675,298 ("the '298 application").

74. The '933 patent issued from United States Patent Application No. 487,774 ("the '774 application"), filed June 7, 1995. The '774 application is a continuing application of United States Patent Application No. 202,874 ("the '874 application"), filed February 28, 1994, which in turn is a continuing application of United States Patent Application No. 113,178 ("the '178 application"), filed October 23, 1987, which is a continuing application of United States Patent Application No. 675,298 ("the '298 application").

75. The '698 patent issued from United States Patent Application No. 468,381 ("the '381 application"), filed June 6, 1995, which is a continuing application of the '179 application.

76. The '349 patent issued from United States Patent Application No. 468,369 ("the '369 application"), filed June 6, 1995, which is a continuing application of the '179 application.

77. The '422 patent issued from United States Patent Application No. 08/100,197 ("the '197 application"), filed August 2, 1993. The '197 application is a continuing application of United States Patent Application No. 07/957,073 ("the '073 application"), filed October 6, 1992. The '073 application is a continuing application of United States Patent Application No. 07/609,741 ("the '741 application"), filed November 6, 1990, which is a continuing application of the '179 application.

**b. Teaching and description of the patents**

78. A person of ordinary skill in the art in 1983-84 would have understood the teachings of the patents-in-suit ("The Lin Patents") to be broader than the specific examples described in the patents.

79. The specification of the Lin Patents describes the DNA sequence(s) corresponding to the human EPO gene and teaches how to isolate it.

80. A person of ordinary skill in the art in 1983-84 would have understood that, based upon the specification of the Lin Patents, various promoters were known in the art and could be used in vertebrate and mammalian cells to express human EPO.

81. Based upon the disclosure of the Lin Patents, a person of ordinary skill in the art in 1983-84 would have understood that various vertebrate and mammalian cells could be used to produce human EPO.

82. The Lin Patents describe and teach how to create vertebrate cells containing multiple copies of the human EPO gene.

83. The Lin Patents describe and teach more than one method to create vertebrate cells containing multiple copies of the human EPO gene.

84. The Lin Patents describe and teach how to produce EPO from vertebrate cells that contain multiple copies of the human EPO gene.

85. The Lin Patents teach how to prepare pharmaceutical compositions of EPO.

86. The Lin Patents teach how to create vertebrate cells that produce human EPO in excess of the levels recited in the claims of the '349 patent.

87. The Lin Patents teach how to isolate EPO from EPO producing cells.

88. The Lin Patents teach how to prepare and use pharmaceutical compositions containing a therapeutically effective amount of human EPO.

89. In the 1950's, in order to help standardize the results being reported by various laboratories studying various putative preparations of EPO, a "unit" of erythropoietin activity, based on the observation that cobalt chloride can induce erythropoietin production, was defined as that amount of erythropoietic activity equivalent to that induced by 5 micromoles of cobalt chloride administered to a test animal.

90. As different preparations of EPO became available over the subsequent years, rather than having to measure the amount of EPO in such preparations by comparison to the erythropoietic activity of cobalt chloride in a test animal, an International Reference Preparation (IRP) containing EPO was agreed upon as a standard which was administered and distributed, in part, by the World Health Organization.

91. The unitage for each successive EPO IRP standard was based on the original definition of a "unit" and was thus defined indirectly by reference back to the erythropoietic activity induced by 5 micromoles of cobalt chloride.

92. In 1983-84, radioimmunoassays (RIAs), as referenced in the '349 patent, were used to measure the amount of EPO in a sample by measuring the ability of the EPO in the sample to compete with radiolabeled EPO for binding to an antibody raised against purified EPO. The results of such RIAs were consistently reported in terms of "units" or "mU" of erythropoietin.

**c. Restriction requirement**

93. On July 3, 1986, the United States Patent and Trademark Office imposed a restriction requirement that required Amgen to select one of six invention groups for continued examination in the '298 application.

94. Amgen elected claims from Group II of the July 3, 1986 restriction requirement for continued examination in the '298 application, and the other, non-elected claims were withdrawn from further consideration in the '298 application.

95. Claims 1-8 of the '933 patent fall within the scope of Group I of the July 3, 1986 restriction requirement.

96. Claims 9-14 of the '933 patent fall within the scope of Group V of the July 3,

1986 restriction requirement.

97. Claims 1-6 of the ‘349 patent fall within the scope of Group IV of the July 3, 1986 restriction requirement.

98. Claims 1-2 of the ‘422 patent fall within the scope of Group V of the July 3, 1986 restriction requirement.

99. As filed on October 23, 1987, U.S. Patent Application No. 07/113,178 (“the ‘178 application”) contained original claims 1-13, 16, 39-41, 47-49, and 55-57 from the parent ‘298 application, which was in the non-elected Groups I and V of the July 3, 1986 restriction requirement.

100. As filed on October 23, 1987, U.S. Patent Application No. 07/113,179 (“the ‘179 application”) contained original claim 1 from the parent ‘298 application, which was in the non-elected Group I of the July 3, 1986 restriction requirement.

101. The ‘178 application was filed as a result of the restriction requirement imposed by the examiner during prosecution of the ‘298 application.

102. The ‘179 application was filed as a result of the restriction requirement imposed by the examiner during prosecution of the ‘298 application.

103. The ‘178 and ‘179 applications are “divisional applications” under the definitions set out in the United States Patent and Trademark Office’s Manual of Patent Examination Procedure in § 201.06.

**d. Issuance**

104. Amgen is the owner by assignment of the ‘868, ‘933, ‘698, ‘349 and ‘422 patents.

**e. Differences in inventions claimed in various patents.**

105. The ‘868 and ‘698 patents include claims directed to methods for growing genetically manipulated mammalian cells to express glycosylated erythropoietin polypeptides and isolating the expressed polypeptides.

106. The ‘349 patent includes a claim directed to processes for culturing cells to produce specified amounts of human erythropoietin.

107. The ‘933 patent includes claims directed to a glycosylated polypeptide that is the product of the expression of genetically manipulated mammalian cells, pharmaceutical compositions containing such polypeptide product, and methods for using such pharmaceutical compositions.

108. The ‘422 patent includes claims directed to pharmaceutical compositions comprising human erythropoietin purified from mammalian cells grown in culture.

**12. Prior litigation with GI and Chugai**

**a. GI’s activities and agreements with Chugai and BM**

109. In or about 1985, Genetics Institute, Inc. (“GI”) created in the United States an EPO-producing cell line derived from Chinese Hamster Ovary cells (CHO cells) called DN2-3α3.

110. CHO cells are mammalian cells.

111. CHO cells are vertebrate cells.

112. DN2-3α3 cells are mammalian cells.

113. DN2-3α3 cells are vertebrate cells.

114. In 1988, Genetics Institute transferred the DN2-3α3 cell line to Boehringer Mannheim's facility in Penzberg, Germany for use by Boehringer Mannheim to develop and sell EPO in Europe.

**b. Amgen's suits against GI and Chugai**

115. On January 4, 1988, Amgen filed a complaint before the International Trade Commission ("ITC") alleging that Chugai Pharmaceutical Co. of Japan and its U.S. subsidiary, Chugai Pharma U.S.A., Inc. had violated former section 337 of the Tariff Act of 1930 by importing recombinant erythropoietin made by a process covered by Amgen's '008 patent.

116. On January 10, 1989, the ITC administrative law judge made an initial determination that the "claims of the '008 patent do not cover a process which is used to manufacture EPO."

117. The ITC administrative law judge's January 10, 1989 initial determination included the finding that '008 claim 4, directed to prokaryotic or eukaryotic host cells transformed or transfected with an erythropoietin DNA, does not cover a process which is used to manufacture EPO.

118. On October 27, 1987 Amgen sued Chugai and GI in the District of Massachusetts for infringement of Amgen's '008 patent.

119. On December 11, 1989, GI and its use of the DN2-3α3 cell line in the United States was found to infringe at least claims 2 (DNA) and 4 (eukaryotic host cells containing specified DNA) of Amgen's '008 patent by this Court.

120. On December 11, 1989, GI lost its claim of prior inventorship of Amgen's '008 patent claims.

121. This Court previously found that: "[t]he successful cloning of the EPO gene took place in September or early October, 1983"; "[o]n February 13 and 14, 1984, Amgen conducted experiments to show that the recombinant human EPO produced in the COS cell was biologically active"; and "[f]rom March 1-9, 1984, Amgen conducted an in vivo bioassay and determined that the recombinant EPO was biologically active." *Amgen Inc. v. Chugai Pharm. Co.*, 1989 WL 169006, at *16 (D. Mass. Dec. 11, 1989).

122. The Federal Circuit affirmed this Court's ruling. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991).

**c. Patent interferences**

123. On 5/9/1989, the U.S. PTO declared Interference No. 102,096 between GI's Fritsch App. No. 06/693,258 and Amgen's Lin Patent No. 4,703,008.

124. The interference count in Interference No. 102,096 was directed to a purified and

isolated EPO DNA sequence.

125. Interference No. 102,096 was decided favorably to Amgen's Dr. Lin and released on 2/3/1992.

126. On 5/9/1989, the U.S. PTO declared Interference No. 102,097 between GI's Fritsch App. No. 06/693,258 and Amgen's Lin App. No. 07/113,179.

127. The interference count in Interference No. 102,097 was directed to a process for the preparation of certain glycosylated polypeptides with the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells.

128. Interference No. 102,097 was decided favorably to Amgen's Dr. Lin on 12/3/1991.

129. On 2/9/1990, the U.S. PTO declared Interference No. 102,334 between GI's Fritsch App. No. 06/824,688 and Amgen's Lin App. No. 07/113,178.

130. The interference count in Interference No. 102,334 was directed to a non-naturally occurring glycoprotein product of the expression of an EPO DNA sequence in a non-human eukaryotic host cell.

131. Interference No. 102,334 was decided favorably to Amgen's Dr. Lin on 12/3/1991.

132. Following the December 3, 1991 interference decisions by the United States Patent and Trademark Office ("PTO"), Genetics Institute filed an appeal to the District of Delaware on February 20, 1992. Genetics Institute appealed the PTO's decision in favor of Amgen in Interference No. 102,097 and Interference No. 102,334, but did not appeal Interference No. 102,096.

133. After conclusion of Genetics Institute's Appeal of Interference No. 102,334 in favor of Amgen's Dr. Lin, prosecution resumed thereafter on Amgen's Lin App. No. 07/113,178.

134. After conclusion of Genetics Institute's Appeal of Interference No. 102,097 in favor of Amgen's Dr. Lin, prosecution resumed thereafter on Amgen's Lin App. No. 07/113,179.

135. The Acting Commissioner of Patents and Trademarks explicitly approved a communication from an examiner of U.S. Patent 5,547,933 deeming the subject matter of the three *Fritsch v. Lin* interferences (Interferences Nos. 102,096, 102,097 and 102,334) patentably distinct.

136. On November 20, 1992 the PTO declared an interference with a pending Chugai application and Amgen's Lin Patent Application No. 609,741.

137. On December 14, 1992 the PTO ruled in favor of Dr. Lin's '741 application.

138. On March 31, 1995 the PTO suspended prosecution of Dr. Lin's Patent Application No. 08/100,197 application due to a potential interference with U.S. Patent No. 4,806,524. U.S. Patent No. 4,806,524 lists Chugai Siyaku Kabushiki Kaisha as the assignee.

139. On January 26, 1999 the PTO declared no interference with U.S. Patent No.

4,806,524 and prosecution of Dr. Lin's '197 application resumed thereafter.

**d. GI/Chugai settlement**

140. On May 12, 1993 Amgen, Inc., GI and Chugai entered into a Settlement Agreement, dismissing counterclaims and entering judgment in Amgen's favor in district courts in Massachusetts, California and Delaware. Pursuant to the Settlement Agreement it was Ordered, Adjudged and Decreed in the District Court of Massachusetts by Judge Young that the " '008 patent was duly and legally issued, valid and enforceable in law and equity, . . . ." *Amgen Inc. v. Genetics Inst.*, 877 F. Supp. 45, 47 (D. Mass. 1995).

**e. GI- Roche relationship and GI-Chugai relationship**

141. The DN2-3α3 cell line used by Roche to manufacture epoetin beta in Penzburg, Germany was originally created and supplied by Genetics Institute, Inc ("GI").

142. GI created the DN2-3α3 cell line and licensed it to Boehringer Mannheim.

143. In 1997, Roche acquired Boehringer Mannheim and all rights to make and use the DN2-3α3 cell line to make and sell epoetin beta, a glycosylated recombinant human erythropoietin, in Europe.

144. Roche's manufacture of rEPO (epoetin beta) in Europe is or was under license from GI.

145. Effective October 1, 2002 the Roche Group acquired a majority ownership of Chugai Pharmaceuticals Co., Ltd ("Chugai").

146. Roche currently owns a controlling interest in Chugai.

**f. Genentech – Roche relationship**

147. In September 1990, Genentech, Inc. ("Genentech") merged with Roche Holding Ltd., a subsidiary of Roche Basel, and Roche acquired a majority ownership interest in Genentech.

148. Roche currently owns a majority ownership interest in Genentech.

**13. Prior Kirin-Amgen litigation with Roche**

**a. Australian settlement**

149. Kirin-Amgen, Inc. a 50-50 joint venture between Amgen, Inc. and the Japanese company Kirin Brewery Company, Limited, was formed in 1984.

150. Roche, Johnson & Johnson (which owns Ortho), Genetics Institute, Inc., and Kirin Amgen, Inc., signed a Settlement Agreement, dated June 1, 2001 to settle "various litigation actions in a variety of countries."

151. The June 1, 2001 Settlement Agreement provided in part: "J&J and K-A grant ROCHE and GI a sixty (60) day option, exercisable in writing, to settle their disputes with respect to the K-A Patents and GI Patents in Australia under the following terms: . . . (ii) ROCHE and GI acknowledge the validity of the K-A Patents . . . ."

152. On June 28, 2001, Roche exercised its option under the June 1, 2001 Settlement

Agreement to settle disputes with respect to the "K-A Patents."

153. The June 1, 2001 Settlement Agreement defines "K-A Patents" as follows: "'K-A Patents' shall mean EP 0148605 and its counterpart patents, including, but not limited to, any patent that has the same disclosure, and any extensions of the like thereof."

154. Each of the patents-in-suit in the present case has the same disclosure as EP 0148605.

**14. CERA Infringement**

155. Roche manufactures and sells NeoRecormon® in locations outside the United States.

156. The active ingredient in NeoRecormon® is epoetin beta.

157. Epoetin beta is a glycosylated recombinant human erythropoietin.

158. Roche makes epoetin beta in Penzberg, Germany.

159. Epoetin beta is produced by the recombinant CHO cell line DN2-3α3 in suspension culture.

160. Epoetin beta is used in Europe for the treatment of anemia associated with chronic renal failure.

161. Epoetin beta has the *in vivo* biological property of causing bone marrow cells to increase the production of reticulocytes and red blood cells.

162. Epoetin beta's amino acid sequence is identical to the amino acid sequence from positions +1 through +165 of Figure 6 of the Lin Patents.

163. Epoetin beta is a glycoprotein.

164. Epoetin beta is a glycosylated erythropoietin polypeptide.

165. Epoetin beta is produced by the recombinant CHO cell line DN2-3α3.

166. Epoetin beta is produced by cells that contain an exogenous DNA sequence encoding human EPO.

167. DN2-3α3 cells comprise transcription control DNA sequences, other than human transcription control sequences, which control transcription of DNA encoding EPO.

168. Roche's DN2-3α3 cells contain a DNA sequence encoding the mature erythropoietin amino acid sequence (+1 through +166) depicted in Figure 6 of the '698 patent, including DNA encoding an arginine at position 166.

169. Roche's DN2-3α3 cells contain the amplified marker gene Dihydrofolate reductase ("DHFR").

170. Roche's DN2-3α3 cells contain amplified copies of the DNA sequence encoding the mature erythropoietin amino acid sequence of Figure 6 of the Lin Patents.

171. Epoetin beta is made by growing DN2-3α3 cells in culture under suitable nutrient conditions.

172. Roche's DN2-3α3 cells secrete glycosylated EPO into the cell culture medium.

173. DN2-3α3 cells are capable upon growth in culture of producing EPO in the medium of their growth in excess of 100U of erythropoietin per $10^6$ cells in 48 hours as determined by radioimmunoassay.

174. Glycosylated EPO is isolated and purified after being expressed from the DN2-3α3 cells.

175. The manufacture, use, sale, offer for sale, or importation in the United States of NeoRecormon® would constitute an act of infringement under any of the asserted claims of Amgen's patents-in-suit.

176. Roche is seeking approval from the United States Food and Drug Administration to sell a pharmaceutical product called MIRCERA®.

177. Roche submitted a Biologic License Application (BLA) with the U.S. Food and Drug Administration on April 19, 2006 regarding MIRCERA®.

178. MIRCERA® is a pharmaceutical composition.

179. The active drug substance in MIRCERA® is methoxy polyethylene glycol-epoetin beta, which Roche has also referred to as "PEG-EPO," "pegylated epoetin beta," "CERA," and "RO0503821."

180. MIRCERA® stimulates red blood cell production.

181. MIRCERA's chemical name is methoxy polyethylene glycol-epoetin beta, with code designations RO0503821 (drug substance) and Ro 050-3821 (drug product).

182. RO0503821 is manufactured and tested at Roche Diagnostics GmbH Penzberg (Germany).

183. Roche fills glass vials or pre-filled syringes (PFS) with MIRCERA® in Switzerland and Germany, respectively.

184. Epoetin beta is a starting material for Roche's RO0503821 drug product.

185. peg-EPO is a conjugate of one methoxy-polyethylene glycol (PEG) molecule to one EPO molecule.

186. The pegylation reaction to produce peg-EPO causes a covalent attachment in the form of an amide bond between the peg moiety and either the N-terminus of epoetin beta or the ε-amino group of an internal lysine residue of epoetin beta.

187. In addition to peg-EPO, Roche's MIRCERA® pharmaceutical composition is further comprised of an aqueous solution containing sodium phosphate, sodium sulphate, mannitol, methionine, and poloxamer 188.

188. The MIRCERA® pharmaceutical composition comprises a pharmaceutically acceptable diluent.

189. Water for injection is a diluent.

190. Roche's peg-EPO product is comprised of recombinant human EPO.

191. Roche's peg-EPO is comprised of epoetin beta.

192. Roche's peg-EPO product has the identical amino acid sequence as epoetin beta.

193. peg-EPO contains the same carbohydrate structure as epoetin beta.

194. peg-EPO contains an erythropoietin glycoprotein product.

195. Neither peg-EPO nor epoetin beta occur in nature.

196. MIRCERA® is not naturally occurring.

197. The peg in peg-EPO is inert.

198. Unconjugated polyethylene glycol cannot bind to EPO receptors or stimulate erythropoiesis.

199. Roche's peg-EPO binds to the EPO receptor on erythroid progenitor cells.

200. peg-EPO and epoetin beta activate the same signaling pathways within red blood cell progenitors when they bind to the EPO receptor.

201. peg-EPO has the *in vivo* biological activity of causing bone marrow cells to increase production of reticulocytes and red blood cells.

202. Roche's peg-EPO is a therapeutically effective treatment for anemia associated with chronic kidney disease.

203. Roche's MIRCERA® vials and pre-filled syringes contain a therapeutically effective amount of human erythropoietin.

204. Roche's peg-EPO has substantially the same pharmacologic effect as EPO.

205. Pegylation is a conventional process used to alter the clinical properties of biologically active products.

206. Before Roche's development of MIRCERA®, pegylation was a known technique to increase the circulating half-life of recombinant protein drugs.

**15. Roche's Defenses**

**a. '008 patent**

207. No DNA sequence encoding human EPO had been publicly disclosed as of December 1983.

208. U.S. Patent Application Serial Nos. 675,298 (November 30, 1984), 655,841 (September 28, 1984), 582,185 (February 21, 1984), and 561,024 (December 13, 1983) had not been publicly disclosed as of December 1984.

209. A U.S. Patent and Trademark Office examiner considered whether the '868 patent claims were patentably distinct from earlier-issued claims of U.S. Patent No. 4,703,008, and nonetheless allowed the '868 patent claims.

210. A U.S. Patent and Trademark Office examiner considered whether the '349 patent claims were patentably distinct from earlier-issued claims of U.S. Patent No. 4,703,008, and nonetheless allowed the '349 patent claims

**b. Lai/Strickland '016 patent**

211. Although they issued after the Lai/Strickland '016 patent, U.S. Patent Nos. 5,547,933, 5,756,349, 5,955,422, 5,441,868, and 5,618,698 ("the patents-in-suit") all

claim priority from applications, including the '298 application, that were filed before the June 20, 1985 filing date of the Lai/Strickland '119 application.

212. Dr. Lin's U.S. Patent No. 4,703,008 was filed earlier than the Lai/Strickland '016 patent but issued later than the Lai/Strickland '016 patent.

213. The inventions claimed in the Lai/Strickland '016 patent were not conceived as of the November 30, 1984 filing date of the '298 application.

214. During the term of the Lai/Strickland '016 patent, one could make, use, sell, offer for sale, and import into the United States recombinant erythropoietin without infringing claim 10 of the Lai/Strickland '016 patent.

215. During the period from June 20, 1985 to May 19, 1987, when the Lai/Strickland '016 patent was being examined by the U.S. Patent and Trademark Office, Amgen accelerated prosecution of the '298 application.

216. During prosecution of U.S. Patent Application No. 07/113,178, which gave rise to the '933 patent-in-suit, a U.S. Patent and Trademark Office examiner determined that the pending claims were patentably distinct from earlier-issued claims of the Lai/Strickland '016 patent.

217. During prosecution of U.S. Patent Application No. 07/113,179, which gave rise to the '868, '698, '349 and '422 patents-in-suit, a U.S. Patent and Trademark Office examiner determined that the pending claims were patentably distinct from earlier-issued claims of the Lai/Strickland '016 patent.

**c. Inequitable conduct**

218. Examiner Martinell issued all the patents-in-suit, as noted by the face of each patent.

219. Examiner Martinell was the examiner in PCT Application US84/02021 who issued the International Search Report, submitted as Exhibit 1 in the 4/23/1986 Preliminary Amendment Accompanying Petition to Make Special Because of Actual Infringement of the '298 application.

220. Examiner Martinell was an examiner in U.S. Patent Application No. 06/582,185, filed 2/21/1984, which is a continuation-in-part of U.S. Patent Application No. 06/561,024, filed 12/13/1983.

221. On September 7, 1994, Examiner Martinell conducted two consecutive personal interviews with representatives of Amgen regarding the '179 application and the application continued from the '178 application, during which the application rejections in each application were discussed.

222. Lin *et al.*, *Cloning and Expression of the Human Erythropoietin Gene*, 82 Proc. Nat'l Acad. Sci., 7580, 7582 (1985)) ("Lin PNAS Publication") is listed on the face of the United States Patent No. 5,547,933 ("'933 Patent").

223. The Lin PNAS Publication reports, "The secreted Epo has an apparent *M*, of 34,000 when analyzed in an electrophoretic transfer blot."

224. During the 102,096 ("'096"), 102,097 ("'097), and 102,334 ("'334") interference proceedings, Egrie, *et al.*, 1986 Characterization and Biological Effects of Recombinant Human Erythropoietin, *Immunobiol.*, vol 172, pp. 213-224 (1986) ("Egrie 1986 Publication") was offered into evidence.

225. The Egrie 1986 Publication contains the same SDS-PAGE gel that Amgen submitted to the FDA in Amgen's Notice of Claimed Investigational Exemption for Recombinant Human Erythropoietin (r-HuEPO).

226. During the '096, '097, and '334 interference proceedings, portions of the lab notebook of Dr. Joan Egrie (including the "Egrie Input file") were offered into evidence.

227. During the '096, '097, and '334 interference proceedings, Amgen's Product License Application for r-HuEPO was offered into evidence.

228. The Board of Patent Appeals and Interferences ("Interference Board") considered the Product License Application in reaching its final decision in the '334 Interference.

229. During the '096, '097, and '334 interferences, the Browne 1986 Publication was offered into evidence. This publication reports:

> The r-hEPO produced in COS-1 cells is indistinguishable from urinary EPO by Western blot analysis (Egrie et al. 1985).
>
> …
>
> Human urinary EPO and CHO-cell-derived r-hEPO migrate identically in SDS-polyacrylamide gels, indicating that both molecules are glycosylated to a similar extent. …Trace amounts of *N*-aceylgalactosamine were found in r-hEPO, indicating the presence of O-linked glycosylation.
>
> …
>
> ..Although the presence of *N*-acetylgalactosamine had not been detected previously (Dordal et al. 1985), these results demonstrate that urinary EPO, as well as r-hEPO, contains O-linked carbohydrate…In addition, direct carbohydrate analysis of endoglycosidase-F-treated r-hEPO yields galactose, sialic acid, and *N*-acetyl galactosamine, confirming the presence of O-linked carbohydrate (T.W. Strickland et al., in prep.). As shown in Figure 4, the proportion of EPO containing O-linked carbohydrate is comparable in urinary EPO and r-hEPO.

230. During the prosecution of '933 Patent, Examiner Fitzgerald reviewed the record and opinion of the '334 interference proceedings. His notes state that he reviewed parent file 675,298, interference file # 102, 334, published Intf. Decisions (Fritsch v. Lin) & Amgen v. Chugai (18 U.S.P.Q. 2d at 1016) Oct – Nov. 1993 and Fitzgerald DL.

231. During the prosecution of United States Patent Application No. 202,874 ("'874 application"), parent to the '933 Patent, Browne, *et al.*, "Erythropoietin: Gene Cloning, Protein Structure, and Biological Properties," *Cold Spring Harbor Symposia on Quantitative Biology*, vol. L1, pp. 693-702 (1986) ("Browne 1986 Publication") was

submitted as an attachment to the office action response dated February 16, 1995 submitted to the Patent Office.

232. Amgen notified the Patent Office of the *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, Civil Action No. 97-10814-WGY (D. Mass. filed Apr. 15, 1997) on April 16, 1997.

233. The Declaration of Thomas W. Strickland, dated Feb. 13, 1992 ("1992 Strickland Declaration") provides experimental data on the presence of O-linked glycosylation on and monosaccharide content of recombinant human EPO produced in CHO cells by Amgen in 1985, and does not compare rEPO with uEPO, from the standpoint of molecular weight, carbohydrate composition or otherwise.

234. The Declaration of Thomas W. Strickland, dated May 19, 1994 ("1994 Strickland Declaration") does not compare rEPO with uEPO, from the standpoint of molecular weight, carbohydrate composition or otherwise, or even mention uEPO.

235. Takeuchi, *et al.*, *Comparative Study of the Asparagine-linked Sugar Chains of Human Erythropoietins Purified from Urine and the Culture Medium of Recombinant Chinese Hamster Ovary Cells*, J. Biol. Chem. 263(8) (1988) ("Takeuchi *et al.*") was disclosed to the Interference Board during the '096, 097, and '334 interferences, and is referenced on the face of the '933 patent, evidencing that it was disclosed to and considered by the examiner. This publication reports in part:

> "Analysis of the monosaccharide composition of HuEPO performed in our laboratory confirmed the occurrence of one N-acetylgalactosamine residue, indicating that one O-linked sugar chain is included in recombinant Hu-EPO."

236. Sasaki, *et al.*, *Carbohydrate Structure of Erythropoietin Expressed in Chinese Hamster Ovary Cells by a Human Erythropoietin cDNA*, J. Biol. Chem. 262, 12059-76 (1987) ("Sasaki *et al.*") was disclosed to the Interference Board during the '096, 097, and '334 interferences, and is referenced on the face of the '933 patent, evidencing that it was disclosed to and considered by the examiner.

237. Examiner Martinell discussed Takeuchi *et al.* in an office action in the prosecution of the '933 Patent.

238. Examiner Martinell had before him Takeuchi *et al.* and Sasaki *et al.*

239. Both this Court and the Federal Circuit held that Amgen had no intention of deceiving the Patent Office by withholding information regarding the difference between rEPO and uEPO. *Amgen v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 145 (D. Mass. 2001), *aff'd in relevant part*, 314 F. 3d 1313 (Fed. Cir. 2003).

240. During the prosecution of the '179 application, Amgen provided the Federal Circuit's decision in *Amgen Inc. v. U.S. Int'l Trade Comm'n*, 902 F.2d 1532 (Fed. Cir. 1990) to the Patent Office.

241. Amgen's Statement of Grounds of Opposition of Genetics Institute's EP 411 678 ("'678 patent) explained why, based on the disclosure and teachings of Dr. Lin, Amgen's European patent EP 148,605 anticipated that which GI had attempted to claim in Europe in its '678 patent, including EPO with O-linked glycosylation.

242. Amgen argued during the ‘096 and ‘097 Interference that the two separate counts corresponding to the claims of the ‘008 patent and the ‘179 applications respectively were not the same invention.

243. Amgen argued during the ‘097 Interference that the process Count was not obvious.

244. The inventions claimed in the ‘178 and ‘179 applications were considered to be patentably distinct by the PTO.

245. The references upon which rejections in the ‘179 and ‘178 applications were based are listed in Information Disclosure Statements (“IDS”) submitted to the Patent Office in both the ‘179 and ‘178 applications’ prosecution.